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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/648,547 | 08/25/2003 | Abraham Mittelman | 12354/9 | 5161 |

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| EXAMINER | |
|---|---|
| DIBRINO, MARIANNE NMN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/648,547 | MITTELMAN ET AL. | |
| | Examiner | Art Unit | |
| | DiBrino Marianne | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *2,8 and 13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/13/04*. 3/28/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to Comply with the Sequence Rules.

## DETAILED ACTION

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

**Full compliance with the sequence rules is required in response to this Office Action. A complete response to this Office Action should include both compliance with the sequence rules and a response to the Office Action set forth below. Failure to fully comply with both these requirements in the time period set forth in this Office Action will be held non-responsive.**

2. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, the brief description of the drawings for Figure 1, page 8 at [0027], page 14 at [0045] and page 20 at [0050]).

3. Applicant's response filed 3/28/06 is acknowledged and has been entered.

4. Applicant's election of Group II (claim 3), and species of "examining amino acid sequences within the antigen for binding to an MHC class II molecule by a predictive method of comparing amino acid sequences within the antigen to a consensus MHC binding sequence," and "examining sequence similarity by comparing overlapping amino acid sequences 5, 6 or 7 amino acid residues in length wherein the short overlapping amino acid sequences are offset by 1 or 2 amino acid residues" in Applicant's said response filed 3/28/06.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claim 3 reads on the elected species.

Accordingly, claim 8 (non-elected species of Group II), claims 2 and 14-19 (non-elected groups I, III and IV) and claim 13 (linking claim for Groups III and IV) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1, 3-7 and 9-12 are currently being examined.

5. It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 10/306,514 and Application No. 60/333,249, filed 11/25/02 and 11/23/01, respectively. A reference to the prior application must be inserted as the first sentence of the specification of this application if Applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

Applicant should amend the first line of the specification to update the status (and relationship) of the priority documents.

The first sentence of the specification should refer to the provisional application using language such as:

This application claims the benefit of U.S. Provisional Application No. 60/____, filed ____. See MPEP 1302.04
If a statutory reference is included in this statement, if must be to 35 USC 119(e) and not to 35 USC 120.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP. 602.01 and 602.02.

The oath or declaration is defective because: there is no residence or post office addresses given for Inventor Kanduc, nor is a country of citizenship provided.

7. The abstract of the disclosure is objected to because there is text at the top and bottom of the page separate from the abstract paragraph. In addition, the wrong page number appears. Correction is required. See MPEP § 608.01(b).

8. The drawings are objected to because the figures have handwritten changes. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the Examiner, the

applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

9. The disclosure is objected to because of the following informalities:

a. the claim pages have two sets of page numbers that are different.

b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 13 at [0040]. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction(s) is/are required.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 4 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the claimed method of identifying an immunodominant epitope of an antigen wherein the binding *affinity* is predicted by comparing amino acid sequences within the antigen to a consensus MHC binding sequence.

The instant claims encompass a method wherein binding *affinity* is predicted by comparing amino acid sequences within the antigen to a consensus MHC binding sequence. There is insufficient disclosure in the specification on such a method.

The specification discloses that in one embodiment of the invention, MHC binding, not MHC binding affinity, is predicted by comparing amino acid sequences within the antigen to a consensus MHC binding sequence ([010]).

Given the failure of the specification to disclose a method step of predicting binding affinity by comparing amino acid sequences within the antigen to a consensus MHC binding sequence, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

12. Claims 4 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not disclose how to use the claimed method of identifying an immunodominant epitope of an antigen wherein method step of predicting the binding *affinity* is predicted by comparing amino acid sequences within the antigen to a consensus MHC binding sequence. The specification has not enabled the breadth of the claimed invention because the claims encompass predicting binding affinity rather than binding with the said method step. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed method step can be used for such a purpose.

The specification discloses no working examples with regards to using comparison of amino acid sequences within the antigen to a consensus MHC binding sequence to predict MHC binding *affinity*.

The specification discloses that in one embodiment of the invention, MHC binding, not MHC binding affinity, is predicted by comparing amino acid sequences within the antigen to a consensus MHC binding sequence ([010]).

Evidentiary reference Rammensee *et al* (Immunogenetics, 1999, 50: 213-219, IDS reference) teaches that the SYFPEITHI program may be used to predict a relative probability and strength of binding, *i.e.,* a prediction of binding affinity, of a peptide sequence to an MHC molecule based upon giving the amino acid residues of a candidate peptide a specific value depending upon whether the said amino acid residues are anchor, auxiliary anchor, preferred or negative binding amino acid residues (see entire article).

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 3-7 and 9-12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claims 1, 3-7 and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the testing of the candidate immunodominant epitope for immunodominance.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1, 3, 5-7 and 9, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Natale *et al* (Imm. Cell. Biol. 2000, 78: 580-585, IDS reference).

Natale *et al* teach examining amino acid sequences within the HPV16 E7 oncoprotein for binding to MHC class II molecules, and examining amino acid sequences within the said oncoprotein to determine sequence similarity to the host proteome. The low similarity 23-mer peptide from said oncoprotein was analyzed by testing peptides of 15 amino acid residues in length for binding to MHC class I molecules, then creating 5-mer peptide subsequences of the said peptides that bind, said 5-mer peptides overlap by one amino acid residue, and analyzed them for human matches, *i.e.*, for similarity to the host proteome. Natale *et al* teach that the E7 sequence 44-62 is also the E7 peptide hosting the lowest number of matches to human proteins, and that the peptides made of sequences absent and/or underrepresented in the host's self proteins may be the immunogenic peptides useful for immunotherapeutic cancer treatment (last two paragraphs of article on page 584).

18. Claims 1, 3, 5-7, 9, 10 and 12 are rejected under 35 U.S.C. 102(a) as being anticipated by Kanduc *et al* (Peptides. 2001, 22: 1981-1985).

Kanduc *et al* teach assessing the potential binding of HPV16 E7 oncogene protein subsequences to MHC class II molecules using the SYFPEITHI program and further analyzing them for similarity to the mouse proteome. Kanduc *et al* teach for the latter step, dissecting peptide sequences into 5-mer motifs, or 6-mer overlapping peptides, offset by one residue, for example, MGTLG, GTLGI, TLGIV, *etc,* were used for analyzing the similarity of the sequence MGTLGIVCPICSQKP (Results and Table 1). Kanduc *et al* teach that they identified the linear amino acid sequence recognized by a mouse monoclonal antibody raised against the full length HPV 16 E7 oncoprotein, and that binding strength being equal, the non-self character, *i.e.,* the non-similarity to the host proteome, dictates peptide immunogenicity (especially Abstract and Discussion sections). Kanduc *et al* teach the 15-mer peptide RAHYNIVTFCCKCDS contains the immunodominant epitope, and by using overlapping (by one amino acid residue) 6-mer peptides, they 'produced' the immunodominant peptide AHYNIVTFCCKC, having the highest binding potential to the mouse MHC class II molecule, and a low degree of similarity to the host's proteome (especially paragraph spanning pages 1983-1984).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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